IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: CHOPP ET AL.

Serial No.: 10/018,201 Group Art Unit: 1614

Filed: 04/02/02 Examiner: JAGOE, Donna A

For: NITRIC OXIDE DONORS FOR INDUCING NEUROGENESIS

Attorney Docket No: 1059.00063

Commissioner for Patents
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Sir:

DECLARATION OF MICHAEL CHOPP

I, Michael Chopp, do hereby say that:

1. I am a co-inventor of the invention set forth and claimed in the above-captioned patent application.

2. I am an expert in the field of neurogenesis.

3. I have reviewed in detail the Office Action issued October 19, 2005. Specifically, I have reviewed the rejection of claims 1-8 as being unpatentable over the Moskowitz patent.

4. The Office Action states that the Moskowitz patent teaches a method of treating strokes and the resulting neurological damage by administering nitric oxide releasing compounds. The therapeutic target of the Moskowitz approach is the reduction of cerebral infarction (i.e. volume of dead brain tissue) after ischemic stroke that is stroke caused by a lack of blood flow to the brain. Moskowitz seeks to increase blood flow to the brain to limit volume of infarction. In other words, the patent discloses treating injured brain in an attempt to salvage brain tissue. The treatment disclosed in the Moskowitz patent is limited to times early after onset of ischemic stroke when blood flow increase can increase the volume of blood flowing to the damaged tissue. In the Moskowitz patent, there is disclosed that the reduction of the infarction is mediated by administration of a substrate for NO before or early (within the first 1-2 hours) after

stroke. The substrate is given from 16 hours before stroke to 2 hours after stroke. This enhances blood flow to the brain and thereby counteracts some of the loss of blood flow initiated by the stroke. The Moskowitz patent states in column 1 line 31 that, "the nervous system lacks the ability to regenerate," in column 1 lines 40- 44, "the ultimate size of the infarct which forms the basis of medical therapy is the extent of vascular support." Thus, according to the Moskowitz patent, the intervention must be designed to improve blood flow and thereby to reduce the ischemic lesion, because when the lesion is complete, the lesion cannot be reduced by treatment there is no benefit.

5. The Moskowitz patent also discloses that the brain cannot regenerate. The data presented in the Moskowitz patent only relate to treatment of a model of ischemic stroke with a substrate of NO. All data presented by Moskowitz show a reduction of volume of cerebral infarction, dilation of blood vessels, and, as noted in column 3 line 18, the approach of the Moskowitz patent is to "limit the extent of stroke-associated infarct." The patent discloses that treatment should preferably begin shortly after the initiation of stroke and preferably at any point in time prior to the completion of the infarction process. There is disclosed that, "treatment may be initiated, however, at any point in time prior to the completion of the infarction process." The disclosure also provides that "in certain instances, the methods of the invention may be used to treat a patient after the completion of a stroke episode." There is no disclosure of what those "instances" are or how they relate to treatment and thus, the disclosure does not enable one of skill in the art to ascertain the possibility that any beneficial effects are afforded a patient who has the NO compound administered post-stroke. Further, there is no disclosure that treatment at any point subsequent to the completion of the stroke would function in the desired manner. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile. Further, the Moskowitz patent and all other prior art disclosures disclose methods for limiting the infarction process or increasing the blood flow to the areas of the brain that were damaged by stroke. There is no disclosure for the regeneration of neurons as is disclosed in the presently pending independent claims.

6. In contradistinction, the presently pending independent claims claim NO donors, PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on the volume of infarction. As disclosed throughout the currently pending patent

application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the treatment. Further, the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy can be administered days and weeks after the injury, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, and can even be administered 24 or more hours after stroke. The method and compound of the presently pending independent claims claim inducing brain remodeling an event that is independent of the reduction of the volume of cerebral infarction. There is no connection or association of reduction of volume of cerebral infarction and with the production of new brain cells. There is no requirement of the presence of a NO donor to induce brain remodeling and functional benefit.

7. Further, new data has been recently generated. This data was obtained by following the methodology disclosed in the Moskowitz patent. The results indicate that the method of the Moskowitz patent does reduce ischemic damage, however, there is no neurogenesis, new neuron growth, that occurs. As stated above, the method of the Moskowitz patent does not create the results that are obtained by the presently claimed invention as set forth in the pending amended independent claims.

8. The data is attached hereto as Appendix A.

9. The Moskowitz patent does state at Column 2, lines 17-22, that the compounds can be administered either before, during, or after the stroke. However, this is an inaccurate statement as the rest of the specification, including all of the examples and all of the knowledge of those of skill in the art indicated that strokes could not be treated post-completion. Specifically, it was determined previously that there was a very small window of time during which a stroke could be treated. The entire purpose of treating stroke during this time was to the limit the amount of infarction. In other words, the doctors would administer a compound in an attempt to begin additional blood flow to the area previously deprived of blood and oxygen to limit the amount of damage that occurred. In fact, my study was the first to either report or suggest treating a stroke post completion.

9. In view of the above, it is my opinion, based on our research results, that one skilled in the art could not utilize the teachings of the cited prior art to derive the

present invention. Rather, we utilized a significantly different approach, not at all utilizing the methods or data set forth in the cited prior art to derive the invention. Thus, we unexpectedly derived the claimed subject matter of the present invention.

The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true.

DATE: December 22, 2005

Michael Chopp